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Workshop Report

Genomics in the land of regulatory science

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ABSTRACT

Genomics science has played a major role in the generation of new knowledge in the basic research arena, and currently question arises as to its potential to support regulatory processes. However, the integration of genomics in the regulatory decision-making process requires rigorous assessment and would benefit from consensus amongst international partners and research communities. To that end, the Global Coalition for Regulatory Science Research (GCRSR) hosted the fourth Global Summit on Regulatory Science (GSRS2014) to discuss the role of genomics in regulatory decision making, with a specific emphasis on applications in food safety and medical product development. Challenges and issues were discussed in the context of developing an international consensus for objective criteria in the analysis, interpretation and reporting of genomics data with an emphasis on transparency, traceability and "fitness for purpose" for the intended application. It was recognized that there is a need for a global path in the establishment of a regulatory bioinformatics framework for the development of transparent, reliable, reproducible and auditable processes in the management of food and medical product safety risks. It was also recognized that training is an important mechanism in achieving internationally consistent outcomes. GSRS2014 provided an effective venue for regulators and researchers to meet, discuss common issues, and develop collaborations to address the challenges posed by the application of genomics to regulatory science, with the ultimate goal of wisely integrating novel technical innovations into regulatory decision-making.

1. Introduction

We live in an era marked by significant developments in the advancement of new technologies and innovations in biomedical and food safety research fields resulting in a dramatic increase in our comprehension of genomics, biochemical mechanisms and pathogen behavior. There is a plethora of new analytical tools; some of these tools offer unprecedented high-throughput capabilities that have revolutionized the way standard laboratory experiments are performed. For example, microarray technologies enable the testing of up to tens of thousands of hypotheses at the DNA, RNA and protein levels in a single experiment (Schena et al., 1995). Notwithstanding these rapid technological advances, it may take years for the adoption and application of these innovations in regulatory decision making processes. As depicted in Fig. 1, the translation process from innovation to application usually takes several steps, often an interplay between science and perception. When a new technology is developed, its utility is primarily assessed by non-regulatory entities, usually academia and product development companies such as pharmaceutical entities. During this process, the initial enthusiasm for the new technology gives way to practical reality in a trial-and-error fashion. At the end of this process, the regulatory community finally gains a better understanding of the technology and how it can be used in a "fit-for-purpose" manner in support of regulatory objectives. While this vetting process is critical, it is not necessarily efficient or rapid. Therefore, one of the major challenges is an objective approach to platforms and mechanisms expediting the innovation-to-regulatory application pathway.

To facilitate this process, in 2010, the U.S. Food and Drug Administration (FDA) launched its Advancing Regulatory Science initiative aimed at developing "new tools, standards, and approaches to assessing safety, efficacy, quality, and performance across FDA-regulated products" (http://www.fda.gov/downloads/

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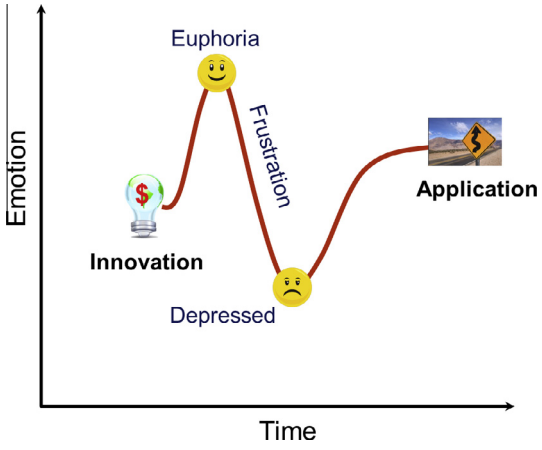

Fig. 1. An illustration of the innovation-to-application process. It usually takes 10–20 years to translate innovation to regulatory application. Therefore, one of the objectives of Regulatory Science Research is to expedite the translation process for innovation by optimizing its reproducibility, standardizing the analysis protocols and promoting data sharing.

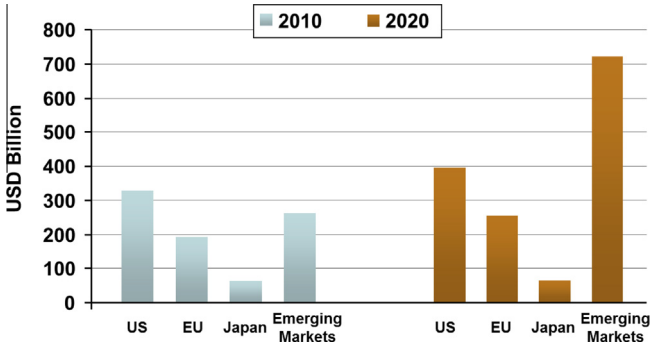

Fig. 2. Pharmaceutical sales in emerging markets are forecasted to outpace US and EU by 2020.

ScienceResearch/SpecialTopics/RegulatoryScience/UCM228444.pdf). The initiative identifies eight scientific areas that affect multiple regulated product domains. The guiding principle of the initiative is to embrace the increased adoption of emerging technologies such as genomics and bioinformatics in regulatory application. As noted by the FDA commissioner (Hamburg, 2011): "Today, we are neither effectively translating scientific discoveries into therapies nor fully applying knowledge to ensure the safety of food and medical products. We must bring 21st century approaches to 21st century products and problems." Regulatory science offers the opportunity to bridge this translational gap.

The FDA, as well as regulatory agencies in other countries, rely on science as the foundation for decision making to fulfill its mission (Woosley, 2013; FSANZ, 2013). Consequently, agencies such as the FDA continuously evaluate new tools for their potential and proper use in the review process. For example, advanced high throughput genomic technologies offer new ways to study disease and toxicity at the molecular level and for discovery of corresponding biomarkers. Even when this technology was in its infancy, the FDA had already started the discussion on how to evaluate these new data streams in supporting the safety and efficacy of new medical products (Goodsaid et al., 2010) and how to develop standards for receiving these new data and ensuring reliable and reproducible results (Tong et al., 2007).

Today's consumer products are increasingly globalized, impacting public health worldwide, posing new challenges for regulatory authorities. For example, imports of drug products into the US have tripled since 2002 (http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/GlobalProductPathway/UCM262528.pdf). The FDA currently regulates 300,000 production facilities in 150 different countries. As shown in Fig. 2, global pharmaceutical sales in emerging markets are anticipated to outpace sales in the US and EU by 2020, in contrast to sales in 2010. Regulatory science must confront these new realities and take an approach that emphasizes global partnerships to evaluate new technologies for regulatory application. More specifically, countries need to work together as partners and collaborate in the development of the tools and adopt technologies needed by regulatory authorities throughout the world.

To that end, the Global Coalition for Regulatory Science Research (GCRSR) was established in 2013 as an initiative of the FDA (Howard et al., 2013; Miller et al., 2013; Slikker et al., 2012) and now involves a broad range of countries and regions. The mission of GCRSR is to foster the uptake of emerging technologies by engaging global regulatory agencies. This international coalition has the objectives of facilitating education, scientific training and scientific exchanges in the field of regulatory science. It focuses on research to support regulatory decision making by identifying and promoting best practices to understand and interpret data from innovative technologies such as genomics. To date, GCRSR discussions have been focused on (1) defining the role of global research collaborations in advancing regulatory science and its impact on public health; (2) exploring the future of Regulatory Science Research as a tool for advancing regulatory science in the areas of food safety and medical products; and (3) developing strategies for training regulatory scientists in a global setting. Consequently, its main activities involve (1) holding workshops and scientific meetings to discuss the development of new technologies and their potential application in regulatory settings; (2) exchanging scholars and students for the purpose of providing education and training; and (3) enhancing the development and use of regulatory science principles. To achieve these goals, the annual Global Summit on Regulatory Science (GSRS) meeting has been instituted. GSRS conferences provide a venue for regulators and researchers to meet and develop collaborations that address the challenges and needs in the interest of advancing regulatory science. Four meetings have been conducted so far, with the first (GSRS2011) taking place in the US (Slikker et al., 2012), the second (GSRS2012) in China (Miller et al., 2013), the third (GSRS2013) in the US (Howard et al.) and the fourth (GSRS2014) in Canada (http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/WhatWeDo/ucm289679.htm). Here we summarize key discussions from the most recent summit, GSRS2014, which took place in Montreal, Canada, on August 21–22, 2014, and focused on the current and future role and challenges of applying genomics in a regulatory context.

2. Genomics in regulatory science – A key focus of GSRS2014

Genomics has attracted widespread attention as an advanced means of studying the underlying molecular mechanisms of disease progression, health and pathogen behavior and relationships. It has also gained attention as an applied discipline to identify novel molecular targets and disease markers for drug development and/or diagnostic purposes, and to address regulatory challenges that are difficult to overcome by conventional methods. Genomics is recognized in the FDA Advancing Regulatory Science (http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM228444.pdf) strategy as well as by regulatory agencies in other countries as a major opportunity for advancing food safety, medical product development (in terms of safety and efficacy), and precision/personalized medicine. Despite

a decade of rapid technical advancements in the field of genomics, the anticipated benefits have been slow to translate into regulatory applications. While the reasons for this slow uptake are multi-factorial, the need for further knowledge discovery and the development of more sophisticated tools to query large data sets are necessary. Perhaps as importantly, the adoption of new genomic technology hinges on the creation of regulatory global partnerships to collaborate, share expertise and determine the extent to which emerging genomics technologies might benefit and serve common regulatory needs. Determining the safety, efficacy, quality, potency and performance of medical products and foods is required by law in the U.S as well as in many other countries. Therefore, the emphasis of GSRS2014 was to address key questions regarding the application of genomics for safety assessments of foods and medical products, and how these questions can be appropriately addressed via collaboration and cooperation in the global context. These questions include (1) the role of genomics in advancing regulatory science in the areas of medical products and food safety; (2) the issues and challenges of applying next-generation sequencing to pathogen detection, identification and characterization; and (3) the role of bioinformatics in advancing regulatory genomics.

The theme of GSRS2014 was "Regulatory Genomics and Beyond." The meeting consisted of four sessions featuring panels of subject matter experts speaking on various themes: session 1, "Genomics and Product Safety," provided a global overview of genomic applications in food safety and medical products among regulatory agencies worldwide; session 2, "Lessons Learned from Applying Genomics to Food Program," emphasized how genomics can enhance regulatory capacity and efficiency for food safety; session 3, "Challenges in Regulatory Genomics," discussed challenges in applying genomics, particularly next-generation sequencing technologies for pathogen identification and outbreak detection; and session 4, "Genomics and Beyond," examined a broad range of topics relating to regulatory genomics, including how to regulate genomics-based diagnostic devices, and the ethical issues and dilemmas faced in genetic testing and policy development. The conference concluded with a panel discussion on (1) how regulatory practices and approaches should be developed around new genomics technologies; and (2) the best practices and guidelines for emerging genomics programs in regulation.

3. Regulatory genomics in food safety and medical products

The role of genomics in food safety through whole genome-sequencing (WGS) was a major theme of GSRS2014. The discriminatory power of WGS approaches in food safety has been increasingly appreciated by regulatory food safety agencies around the world, especially in outbreak recognition and source attribution. Recent advancements in WGS such as next-generation sequencing (NGS) technologies open new possibilities for comprehensive analyses of microbes recovered from inspection samples. It was pointed out that NGS can now render a bacterial genome much faster (i.e., within a working day) and at a significantly lower cost (e.g., less than $100 USD with MiSeq systems by Illumina, www.illumina.com/systems/miseq.html) than previously possible, making it feasible to sequence food-borne isolates in nearly real-time under certain circumstances (e.g., during food-borne illness outbreak investigations). Presenters from regulatory agencies of various countries (e.g., the US FDA's Center for Food Safety and Applied Nutrition and Canadian Food Inspection Agency and Public Health Agency of Canada) outlined the promising regulatory roles of WGS in food microbiology inspection programs including, but not limited to, pathogen identification, outbreak detection, source attribution, and hazard characterization.

In the course of the ensuing discussions, various challenges to the full implementation of WGS in regulatory food safety applications were recognized. As with conventional microbiological typing tools, genomic applications have also had to undergo substantial evaluations for reliability and reproducibility as they are integrated into regulatory decision-making processes. Although processes can always be improved, studies of this nature have shown that whole genome sequencing is fit for purpose for foodborne pathogen traceability and have included proficiency across a distributed network of end-users, evaluation of consistency across various sequencing platforms, and validation of the bioinformatics pipelines deployed to cluster resultant "big data". The U.S. FDA's GenomeTrakr Network represents one example of a distributed network of next-generation DNA sequencers that is focused on enhancing food safety. In many ways, the current paradigm shift in molecular subtyping to genomic approaches has been reminiscent of the challenges faced by FDA and other federal public health agencies during previous deployments of subtyping tools such as pulsed-field gel electrophoresis (PFGE) which remains in use still today by many laboratories.

One important outcome of GSRS2014 is recognition that genomics science is rapidly evolving and progressing, and that there are already examples of its utilization in support of regulatory food safety investigations worldwide. By contrast, standardization of regulatory practices with new technologies and interpreting the information which is derived from them may take more time. Therefore, the question was raised about how regulatory practices and standards should cope with the fast paced evolution of WGS technology. This issue needs to be addressed at multiple levels such as development of standard practices, data sharing and training. Some argued that such a challenge should not be a barrier to the use of genomics in regulation. The ability to discern the entire genetic blueprint of a foodborne bacterial isolate by WGS offers an unprecedented level of detailed analysis not achievable using conventional techniques such as PFGE, PCR and even microarrays, providing enhanced discriminatory power and new opportunities for assessing the safety of products. The general consensus at the meeting was that this powerful new technology should be fully embraced to execute the most comprehensive analyses leading to the generation of highly informative test results to underscore regulatory decisions. To uphold this vision, it is of great importance that the procedures and processes used to inform risk management decisions be transparent, reliable, reproducible and auditable.

While microbial genomics (including antimicrobial resistance) and food safety received significant attention in GSRS2014, the role of genomics in medical product development and approval was also discussed. There was a particular emphasis on issues relating to applicability of genomics in personalized (aka precision) medicine. As drug makers move toward the development of therapeutics requiring knowledge of the patient's genetic make-up, there will be a greater demand for technology innovation, underscoring the need for increased partnerships between the private sector, academia and regulatory agencies. Pharmacogenomics (PGx) offers the potential to discover new biomarkers for product safety and efficacy to enhance regulatory science. PGx is defined as "the study of variations of DNA and RNA characteristics as related to drug response" (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002880.pdf) and the FDA has incorporated many such biomarkers in drug labels (http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm). Speakers discussed various regulatory applications of PGx biomarkers with the recognition that some challenges remain such as how to assess the body of scientific evidence to support including a PGx biomarker in drug labels and how to qualify a PGx biomarker for regulatory application (Otsubo et al., 2013). It was recognized that, in some cases, a PGx biomarker relevant to

one subpopulation may not be equally effective for another. Thus, biomarker qualification should carefully consider the weight-of-evidence approach in defining fit-for-purpose applications, which has been emphasized in biomarker qualification programs by FDA (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm230597.pdf) and European Medicines Agency (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004201.pdf). One challenge of identifying a PGx biomarker suitable for regulatory applications is the fact that we are often in a "shades of grey" situation with respect to genotype-phenotype correlation (Lu et al., 2014), which gives rise to significant complexity in linking a PGx biomarker to disease manifestation and/or treatment response. Thus, translating PGx data to clinical utility and drug development requires a strong regulatory science "bridge" that consists of reproducible methodologies to generate reliable data, standard data analysis protocols and consensus within the community to prioritize key factors contributing to disease and drug response.

4. Key issues and challenges in regulatory genomics – A path forward

The GSRS2014 speakers and participants emphasized the importance of bioinformatics as an essential tool in the application of genomics technology in regulatory science. In past decades, both drug development and food safety evaluation have undergone a paradigm shift through substantial investments in genomics platforms to support investigations of disease and toxicity at the molecular level. In addition, the rapid growth of biomedical data and their availability through public domains provides unprecedented opportunities for data mining and knowledge base development to generate new hypotheses and guide experiment designs. These types of data are both voluminous and noisy in content, requiring bioinformatics solutions to extract useful knowledge through data management, analysis, interpretation and the establishment of standards to uphold the integrity of these operations. Specifically, data management strategies should include provisions for long term storage of data to ensure its integrity for legal purposes and retrospective analyses. It was recognized that the assessment of bioinformatics is a complex task requiring significant resources which may be beyond the capacity of individuals to pursue alone. One approach to ensure that appropriate tools are available to all interested parties is to develop consensus among regulatory agencies participating in the GCRSR for the standardization of data management and analysis practices to promote transparency and reproducibility of processes underscoring regulatory decision making. To that end, the GCRSR bioinformatics working group was charged with developing a scientific program focusing on bioinformatics for GSRS2015. Moreover, a technical group governed by the GCRSR bioinformatics working group has undertaken an initiative to determine a best practices approach for the application of bioinformatics in food safety.

Training as a principle means for advancing regulatory science was mentioned at the conference by many speakers and in the panel discussion session. It was well appreciated that genomics is complex, rapidly evolving, and results in the generation of big datasets requiring bioinformatics support. Therefore, there is a need to implement diverse training opportunities to develop skill sets with an iterative process for both regulators and regulated industries. The participants of GSRS14 were introduced to the International Scientists Exchange Program (ISEP). ISEP was developed in support of the US-FDA's regulatory capacity strengthening efforts and provides an opportunity for researchers from developing countries to conduct regulatory research projects at the FDA. The research training experience is focused on learning concepts, skills, and techniques that are critical for scientists to build the regulatory infrastructure needed to be successful in the global context. ISEP enhances the quality of education for scientists through international exchange while exploring the international dimensions of their academic field and promotes international understanding and cross-cultural learning for mentors and participants. The projects offered to participants are designed to teach basic research techniques, i.e., core competencies including laboratory safety, study design, ethics in research, bioinformatics, and data integrity. Sharing information and offering training curricula and technology is critical in supporting the need and improvement of global public health. Training scientists via the GCRSR model is an important step toward advancing regulatory science globally.

5. Summary

The world just observed the 10-year anniversary of the sequencing of the human genome (Venter, 2011). No previous scientific accomplishment has been as celebrated for its potential to improve human health. Despite the initial excitement and promise, and a decade of further research and technical advancement, the anticipated benefits have been slow to impact the regulatory stage to a significant degree. The fulsome exploitation of the blueprint of life will demand continued innovation in technology as well as an enhanced nurturing of regulatory science. The GSRS2014 served as a venue for an important dialogue on the role of genomics in regulatory science and the role of regulatory science in advancing the uptake of genomics. The participants acknowledged the importance of developing regulatory practices and procedures to facilitate application of genomics science on the premise that application of the best science results in the best quality of regulation. To realize the benefit of this "symbiotic relationship" between genomics and regulatory science, we need to overcome many challenges. Some challenges are technical in nature, such as data sharing, analytical protocols and development of standardized protocols. Other challenges are of a logistical nature and can be effectively addressed through GCRSR initiatives such as training programs to support rapid translation of basic science to regulatory application. A distinction in regulatory science roles was recognized in the application of genomics for either food safety or medical products. For the former, the emphasis is on developing principles for pathogen genomics to underscore an enhanced regulatory process of pathogen identification and outbreak detection, while the latter focuses more on developing review principles for the new data stream and its application to personalized medicine and biomarkers. Regardless of the application, the GSRS2014 focused on Regulatory Science Research through embracing a novel thinking process for the effective use of the new genomics analytical paradigm.

Disclaimer

The opinions expressed by the authors do not reflect the opinions or policies of their respective institutions. Any statements in this article should not be considered present or future policy of any regulatory agency.

Conflicts of interest

The authors do not have any conflicts of interest to declare.

Transparency Document

The Transparency document associated with this article can be found in the online version.

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